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| 10/030,417 | 08/14/2002 | Rainer H Muller | 668-59190 | 8775 |

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| EXAMINER | |
|---|---|
| EBRAHIM, NABILA G | |

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| 1618 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/030,417 | MULLER ET AL. | |
| | Examiner | Art Unit | |
| | NABILA G. EBRAHIM | 1618 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *13 November 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-17,20,24-29,31-34 and 38-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17,20,24-29, 31-34 and 38-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**DETAILED ACTION**

The receipt of Applicant's amendments to the claims and remarks dated 11/13/2009 is acknowledged.

**Status of Claims**

Claims 1-17, 20, 24-29, 31-34, and 38-47 are pending in the application.

***Status of Office Action***: Final.

**In view of the new amendments to the claims and/or Applicant's arguments the rejections and objections that are not reiterated in the current Office Action are hereby withdrawn.**

***Claim Rejections - 35 USC § 103***

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-17, 20, 24-29, 31-34, and 38-47 remain rejected under 35 U.S.C.103(a) as being unpatentable over Desai et al WO 98/14174 in (Desai) view of Muller US 5, 858, 410 (Muller).

Desai et al (Patent WO '174) discloses a process for preparation of microparticles or nanoparticles of water insoluble drugs; e.g. paclitaxel, an agent that is insoluble in water and uses polymers such as polylactides and polyglycolides. The drug is dissolved in an organic solvent (page 17, lines l 5-25), a protein such as albumin is added to stabilize the nanoparticles (page 17, lines 31-34) and the mixture is homogenized under high-pressure homogenization (page 18, lines 6-15 and page 51, lines 25). In disclosing a method for making a pharmaceutically acceptable formulation,

Desai discusses sterile-filtration and how drug of particle size less than 200 nm is obtained (page 19, lines 1-16, page 10, lines 24 and page 20, and lines 30-35). The drug particles can be in crystalline or amorphous for (page 13, lines 5-10); details of how to make drug particles of size less than 200 nm are provided. Furthermore, Desai et al also disclose the effect the solvent used has on drug particle size (page 38, lines 5-20) and further discuss the advantage of making the composition in the form of albumin-paclitaxel combination-low toxicity.

Regarding the amendments to the claims, the dispersion which have water-reduced dispersion medium containing less than 80 wt% of water is disclosed in Example 4 wherein the taxol is dispersed in ethanol which is free of water i.e. 0% water.

Regarding including the limitation of "at temperature of 20°C or less" would not further distinguish the instant claims over the prior art since Muller teaches suspending the particles at "room temperature" which is between 20°C to 25°C. Thus the instant claims temperature still overlap with the prior art.

Desai did not disclose the piston-gap homogenizer required in claims 44-47 Muller teaches a method for preparing nanoparticles of drugs e.g., corticoids such as prednisolone (col. 22, lines 40-45), the drug particles having average size of 10-1,000 nanometers made by dispersing solid therapeutically active drugs in a solvent and subjecting the dispersion to high-pressure homogenization in a piston-gap homogenizer (abstract and col. 20, lines 23-30) at room temperature (i.e. under 90 degrees; col. 20, lines 35-40).

Instant claims reciting "water-reduced dispersion medium containing less than 50 wt% of water", the recitation would not distinguish the instant claims over the prior art because Muller teaches a method to make a drug carrier subjecting a solid therapeutically active compound dispersed in a solvent to high pressure homogenization in a piston-gap homogenizer to form particles having an average diameter of 40 nm to 100 nm wherein said active compound is insoluble, only sparingly soluble or moderately soluble in water, aqueous media and/or organic solvents (claim 38), note that the use of the preposition "or" means the exclusion of the aqueous media in the dispersion which is interpreted as a non-aqueous solvent and a percentage of 0% water and consequently, less than 50%. Regarding including the limitation of "at temperature of 20°C or less" would not further distinguish the instant claims over the prior art since Muller teaches suspending the particles at "room temperature" which is between 20°C to 25°C. Thus the instant claims temperature still overlap the range of the prior art.

The new amendments to the claim which recites "temperature below 20°C" and "water content of less than 50%" would not differentiate the claims over the prior art since the temperature as amended includes 19°C or lower which very close to room temperature of 20°C. In addition the amount of water of less than 50% is obvious over both Desai and Muller because Desai teaches paclitaxel is added to methylene chloride. The solution was added to human serum albumin solution. The mixture was homogenized for 5 minutes at low RPM (Vitris homogenizer, model: Tempest I)

(Example 1). Further, Muller teaches the use of glycerol (example 4) while instant disclosure glycerol contains 0% water (see example 13, page 36 of the specification)

Therefore it would have been obvious to one of ordinary skill in the art to make paclitaxel or nanoparticles according to the methods disclosed by Desai and homogenize it in a piston-gap homogenizer because Muller teaches that it is evident that by conversion of the microparticles into nanoparticles by means of a high-energy process, to increase the surface tension to such an extent that as a result the saturation solubility increases greatly (col. 6, lines 19+). The person of ordinary skill would have expected success of having a method of preparing nanoparticles of an insoluble or barely soluble active agent using a high pressure homogenizing process in a piston-gap homogenizer and containing less than 80% of water.

Therefore the invention as a whole would have been prima facie obvious to one of ordinary skill at the time the invention was made.

***Response to Arguments***

Applicant's arguments filed 11/13/2009 have been fully considered but they are not persuasive.

Applicant argues that:

The claims of Muller '410 recite using an "organic solvent" to dissolve the already produced particles. This teaching relates to use of the already produced particles. Furthermore, this teaching on how to use the particles cannot be construed as a teaching for producing the particles.

To respond: Muller in the abstract discloses "Provided is a drug carrier, comprising particles of at least one pure active compound which is insoluble, only sparingly soluble or moderately soluble in water, aqueous media and/or organic solvents". Also, Muller is relied upon for teaching high-pressure homogenization in a piston-gap homogenizer (abstract and col. 20, lines 23-30) at room temperature (col. 20, lines 35-40). Further, a step of further modifying a particle can still be considered a method of producing a particle and not using a particle. For example, a step of coating a particle would be considered a method step of producing a particle and not using the particle.

Muller '410 teaches that the "dispersion principle is cavitation." See column 4, lines 6-7 of Muller '410 Cavitation by definition requires large amount water. This was not found persuasive because Muller teaches cavitation **or** shearing and impact forces (abstract), according to the disclosure; the shearing and impact forces are alternative to cavitation.

In some examples of Muller '410, glycerol is used for serving as an emulsion stabilizer. However, glycerol cannot be considered as a organic solvent medium for high pressure homogenization and its content in all cases is below 16.7%. All other components used are solids (such as mannitol and phospholipon). Mannitol is introduced in form of an aqueous solution. So that there is no organic solvent at all. This was not found persuasive because, even if glycerol is used as a stabilizer -which is not disclosed anywhere in Muller- the compound will also accrue its effect as an organic solvent.

The only mention of a non-aqueous medium (organic solvent) in Muller '410 is in the claims. However, the organic solvent is for dispersing the product particles of claim 1. In other words, the organic solvent is for using the already produced particles, and not as the high pressure homogenization medium for producing the particles. There is no disclosure to the contrary in Muller '410.

This was not found persuasive because Muller's examples disclose using glycerol which is an organic solvent.

Muller '410 teaches away from the claimed invention by requiring a large amount of water (80 to 99 % of water) to provide cavitation and produce the particles.

To respond: again Muller is relied upon for teaching high-pressure homogenization in a piston-gap homogenizer (abstract and col. 20, lines 23-30) at room temperature (col. 20, lines 35-40).

Applicant respectfully submits that the Examiner is incorrect in stating or assuming that Desai disclose a process using only an organic solvent or a water-reduced medium containing less than 50 % water as high pressure homogenization medium. The Examiner improperly ignores the required water addition prior to homogenization. Desai uses throughout the entire disclosure thereof and without exception for high pressure homogenization a medium comprising an organic phase and an aqueous phase, i.e., an emulsion.

This was not found persuasive because Desai did not disclose the use of water in the process of making the particles in different embodiments (see for example 1) which teaches 30 mg paclitxel dissolved in 3.0 ml of human serum albumin solution (1 % w/v).

The mixture was homogenized, then evaporated to get the dispersion and the dispersion was lyophilized. Though emulsions are usually comprised of water and oil, it is noted that emulsions are made of any two immiscible liquids; it is not a must that it contains water. Further, the disclosure of emulsion would not automatically include 50% or more water provided that the instant specification discloses taxol as (poorly soluble in water), polysorbate as (an emulsifier) and water as claimed (50% or less) that are homogenized. These are the same ingredients taught by Desai and which are processed also by homogenization, then the instant method is teaching the same emulsions taught by Desai.

All Examples of Desai use such a serum albumin solution and also an aqueous phase, which aqueous phase in turn is indeed the major component of the medium used for high pressure homogenization and is present in an amount of at least 80 % (v/v) and usually over 90 % (v/v). [See the Examples of Desai.] Thus, Applicant respectfully submits that the Examiner is incorrect in stating or assuming that Desai disclose a process using only an organic solvent or a water-reduced medium containing less than 50 % water as high pressure homogenization medium. The Examiner improperly ignores the required water addition prior to homogenization.

To respond: Applicant is correct that Desai use serum albumin. However, instant claims 6 and 9 disclose the same compound recited as "the homogenized matrix". Note that Desai teaches that the **most common example of carrier proteins is serum albumin** (see page 11). Therefore, using serum albumin by either Desai or instant disclosure is

conventional. Further, the serum albumin as a ***solution*** is only disclosed in example 22 and 23.

The homogenization for 5 minutes at low RPM in a Vitris homogenizer, model Tempest I.Q. in order to form a crude emulsion cited by the Examiner is not high pressure homogenization but just an initial pre-mixing of the drug/organic phase/aqueous phase. As mention further in the Example, if read carefully, thereafter this crude emulsion is transferred into a high pressure homogenizer wherein the relevant high pressure homogenization takes place.

To respond to Applicant: the instant specification teaches that pre-suspension is homogenized at approx. **100** bar to approx. **2000** bar using one or more or many cycles. The pressures to be applied in the high-pressure homogenizer and the number of cycles are a function of the desired fineness of the particles. As a rule, the preparation of nanoparticles requires higher pressures (e.g. **1000** bar or more) and a greater number of cycles. The number of cycles likewise depends on the power density of the homogenizer (e. g. 4-20 except for microfluidizers), See page 20. Therefore, the instant application' definition to homogenization includes Desai's method. In addition, all through Desai's disclosure, the homogenizer used is "high pressure homogenizer", since the homogenizer used by Desai is known in the art as a high pressure homogenizer -regardless of the brand of such machine- and since it is not a microfluidizer then Desai cannot be excluded.

Applicant argues that Muller teaches away because it teaches water over 50% and Desai teaches away because in example 7 of Desai, which deals with the effect of

the phase fraction of organic solvent on the particle size, keeping in mind that it is the object to prepare particles suitable for intravenous injection and thus particles which should be as small as possible.

To respond: Muller is relied upon for teaching the piston-gap homogenizer and to show that the machine is well known in the art and it is not novel to use it making particle comprising an active agent that is sparingly soluble in water and the particles are having designed size. Further, the disclosure of Desai cannot be limited to example 7, however, the example shows a comparison and teaches that increasing the phase fraction increases the diameter size of the particle. The example also teaches that the highest fraction phase used in the example produces particles having diameter of 250 nm which is still encompassed by the instant claims regarding a diameter of 5.6 μm.

Note that "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant. The degree of teaching away will of course depend on the particular facts; in general, a reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant." In re Gurley, 27 F.3d 551,553 (Fed. Cir. 1994). The use of patents as references is not limited to what the patentees describe as their own inventions or to the problems with which they are concerned. They are part of the literature of the art, relevant for all they contain. *In re Heck*, 699 F.2d 1331, 1332—33, 216 USPQ 1038, 1039 (Fed. Cir 1983). A reference may be relied upon for all that it would have reasonable suggested to one having ordinary skill in the art, including nonpreferred embodiments. Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product or because it was not appreciated by those skilled in the art.

Applicant argues that the surprising results produced in the instant disclosure is the use of piston-gap homogenizer in combination with high pressure homogenization medium having a dramatically reduced content of water resulting in dramatically decreased cavitation effect.

This was not found persuasive because at the time of the invention, such homogenizers were well known in the art and were known to be used in making designed particles which obviates the instant subject matter. In addition, avoiding cavitation is not specifically recited as an active step in the claims, but only recited as a result of the homogenization process. Since the prior art teaches the same process, the same result thereof would be expected to occur. The claims as written do not specifically exclude cavitation in the process as argued by applicant. Further, Muller teaches using cavitation or shearing and impact forces with introduction of a high amount of energy (Summary). Thus, Muller teaches a method that excludes cavitation.

***Conclusion***

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

***Correspondence***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NABILA G. EBRAHIM whose telephone number is (571)272-8151. The examiner can normally be reached on 9:00AM - 6:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Nabila G Ebrahim/
Examiner, Art Unit 1618

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618